MINI-REVIEW

Prevention of Chemotherapy-Induced Nausea and Vomiting in Cancer Patients

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Abstract

   The supportive care of patients receiving antineoplastic treatment has dramatically improved over the past few years and development of effective measures to prevent nausea and vomiting after chemotherapy serves as one of the most important examples of this progress. A patient who starts cancer treatment with chemotherapy lists chemotherapy-induced nausea and vomiting as among their greatest fears. Inadequately controlled emesis impairs functional activity and quality of life, increases the use of health care resources, and may occasionally compromise adherence to treatment. New insights into the pathophysiology of chemotherapy-induced nausea and vomiting, a better understanding of the risk factors for these effects, and the availability of new antiemetic agents have all contributed to substantial improvements in emetic control. This review focuses on current understanding of chemotherapy-induced nausea and vomiting and the status of pharmacological interventions for their prevention and treatment.

Keywords: Prevention - chemotherapy - nausea and vomiting - cancer patients

Introduction

   Malignant neoplasms remain a leading cause of death worldwide (Siegel et al., 2014). At the beginning of this century, comprehensive treatment for malignant neoplasm had progressed considerably with advances in molecular targeted therapy, immunotherapy and gene therapy. However, chemotherapy is still the primary treatment. Chemotherapy-induced nausea and vomiting (CINV) is the most common and intolerable adverse event, which impedes or even interrupts the scheduled therapeutic program and severely impairs the efficacy (Hassan and Yusoff, 2010; Janelsins et al., 2013; Keat et al., 2013; nccn, 2014). The goal of each antiemetic therapy is to prevent chemotherapy - induced nausea and vomiting (CINV). Twenty years ago, these were inevitable adverse events of chemotherapy and forced up to 20% of patients to postpone or refuse potentially curative treatment (Jordan et al., 2007).

   Clinical and basic research over the past 25 years has led to steady improvements in the control of CINV. The chemotherapy available in the 1950s and 1960s varied greatly in its capacity to induce emesis. Agents such as vinca alkaloids and 5-fluoruracil were in common usage, and only infrequently caused emesis. In contrast, nitrogen mustard were known for association with emesis. There was some awareness of the problem of CINV, but appreciation of its magnitude was not great (Gralla, 1993).

   Based on the current studies, it is generally believed that 5-HT3 plays a dominant role in acute vomiting, while substance P seems to play a more important role in delayed vomiting (Bergstrom et al., 2011).

   In cisplatin-induced CINV, serum 5-HT3 levels peak at 6-8 h after the administration of cisplatin. At this time-point, the clinical symptoms are obvious and the efficacy of 5-HT3 antagonists is excellent. Neurokinin-1 (NK1) receptor antagonists are effective for both acute and delayed vomiting, especially the latter, on which the studies are also focused. The advent and application of Palonosetron, a second-generation 5-HT3 antagonist, furthers our understanding of the mechanisms of CINV. In contrast to the first-generation 5-HT3 antagonist, it is efficacious in both acute and delayed CINV. If this efficacy is based solely on enhanced binding to the receptors and lengthened half-life, then increased administration frequency or dosage of the first-generation drugs should ensure binding saturation of receptors; however, this is not the case.

   More extensive studies have indicated that the 5-HT3 receptor that binds Palonosetron has allosteric sites, and that internalization occurs following binding, thus inhibiting receptor recycling for up to 2.5h (Rojas et al., 2010; Rojas et al., 2014). Additionally, Palonosetron treats both acute and delayed vomiting via the crosstalk that exists between the 5-HT3 and substance P receptor pathways (Rojas et al., 2014).

   Corticosteroids show good antiemetic efficacy in the prevention of acute and delayed emesis, especially

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when combined with other antiemetic agents. However, their role is sometimes underestimated. Another group of antiemetic, the neurokinin-1 (NK-1) receptor antagonists, has been developed. The first drug in this class, Aprepitant, was approved in 2003 (Hesketh et al, 2003).

Another drug Fosaprepitant in intravenous form was approved for prevention of chemotherapy induced acute and delayed emesis.

Studies have shown that the patients benefit from the use of Aprepitant in combination with standard antiemetic therapy, both in the acute and delayed setting of highly and moderately emetogenic chemotherapy. However, although significant progress has been made with the development of a number of effective and well tolerated antiemetic treatments, CINV remains an important adverse effect of treatment.

History of development of chemotherapy and antiemetic therapy for CINV

1950-60	Nitrogen mustard and Actinomycin D induce severe emesis
1960	Introduction of phenothiazines - antiemetic effect via D2 blockage, Area postrema responsible for emesis by chemotherapy(Barison)
1970s	Introduction of cisplatin, no effective antiemetic therapy available; Metaclopromide found to have antiemetic efficacy
1980s	High dose metaclopromide improves antiemetic response rates; Introduction of steroids in prophylaxis; Studies with Ondansetron
1990s	Introduction of 5-HT3 RA - Milestones in antiemetic therapy
2003	Introduction of palanosetron - Second generation 5-HT3-RA
2003	Approval for first NK-1 RA - Aprepitant
2008	FDA approval of IV NK-1 RA - Fosaprepitant
2011	EMA approval of IV NK-1 RA - Fosaprepitant

Pathophysiology of CINV

The central nervous system plays a critical role in the physiology of nausea and vomiting, serving as the primary site that receives and processes a variety of emetic stimuli. The central nervous system also plays a primary role in generating efferent signals which are sent to a number of organs and tissues in a process that eventually results in vomiting. It was Wang and Borison who first proposed the idea of a vomiting centre (Wang and Borison, 1950).

Mechanism of CINV

Three key components involving area in the hindbrain and the abdominal vagal afferents have been identified. Now a day, it is thought that the existence of anatomically discrete vomiting centres is unlikely (Hesketh, 2008). The locations of neurons that coordinate the bodily functions associated with emesis are spread throughout the medulla,

supporting the notion that a central pattern generator receives indirect input from both the area postrema (chemoreceptor trigger zone) and the abdominal vagus by means of the nucleus tractus solitaries.

Chemoreceptor Trigger Zone (CTZ): The Chemoreceptor Trigger Zone is located in the area postrema at the bottom end of the fourth ventricle. The area postrema has afferent and efferent connections with underlying structures, the subnucleus gelatinosus and nucleus tractus solitaries, receiving vagal afferent fibres from the gastrointestinal tract.

Abdominal vagal afferents: The abdominal vagal afferents appear to have the greatest relevance for CINV. A variety of receptors, including 5-HT, NK-1, and cholecystokinin-1, are located on the terminal ends of the vagus afferents. The receptors lie in close proximity to the enterochromaffin cells located in the gastrointestinal mucosa of the proximal small intestine, which contains a number of local mediators, such as 5-HT, substance P and cholecystokinin.

Neurotransmitters: Research over the past three decades have gradually elucidated the clinical significance of several neurotransmitters in the vomiting process. The neurotransmitters serotonin, substance P and dopamine all appear to play important roles in this process.

Classification of Nausea and Vomiting

CINV can be classified into three categories

Acute Onset Nausea and Vomiting: Occurring within 24 hours of initial administration of chemotherapy. Mainly by serotonin (5-HT) release from the enterochromaffin cells

Delayed Onset Nausea and Vomiting: After 24 hours to 5 days after chemotherapy. Various mechanism - Mainly substance P mediated, disruption of the blood-brain barrier, disruption of the gastrointestinal motility, adrenal hormones (Roila et al., 2002)

Anticipatory Nausea and Vomiting: Occurrence is possible after 1 cycle of chemotherapy. Involves an element of classic conditioning. Triggered by taste, odour, sight, thoughts or anxiety secondary to a history of poor response to antiemetic agents (Roila et al., 2002; Aapro et al., 2005).

Associated Risk Factors

Emetogenic potential of chemotherapy

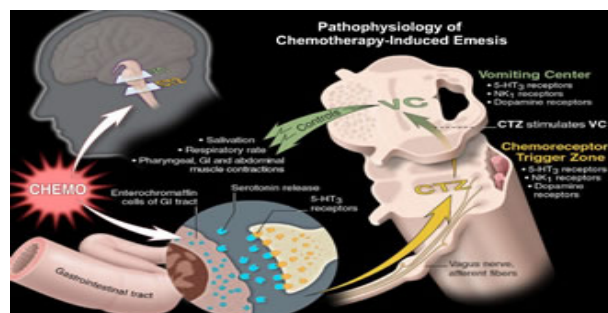It is thought that chemotherapy is the most important

Figure 1. Figure of Mechanism and neurotransmitters

risk factors for the occurrence of CINV. The emetogenic potential of chemotherapeutic agents is classified into four emetic risk groups: high, moderate, low and minimal (Hesketh et al., 1997; Grunberg et al., 2005; Kris et al., 2006).

The emetogenic potential of an antineoplastic therapy varies with specific drug used ranging from cisplatin, which results in severe vomiting in almost all patients, to vinca alkaloids, with only minimal inducible emesis. The chemotherapeutic agents can cause different intention of emesis, depending on the way the drugs are administered.

Patient risk factors

Following is a breakdown of factors that increase susceptibility to nausea and vomiting

Previous experience of poorly controlled emesis: If patients have previous experience of poorly controlled emesis they are more likely to develop post-chemotherapy nausea and vomiting in response to a new treatment. If emesis control was sufficient during previous chemotherapy, the percentage of patients who do not experience emesis in subsequent chemotherapy courses is larger than it is for patients who had insufficient previous

Table 1. Chart of Emetogenic Risk of Intravenous Chemotherapeutic Agents and Oral Chemotherapeutic Agents

Level 1 (minimal risk, <10%)	Level 2 (low risk, 10-30%)	Level 3 (moderate risk, 31–90%)	Level 4 (high risk, >90%)
Intravenous			
Bevacizumab	Asparaginase	Alemtuzumab	Actinomycin D
Bleomycin	Bortezomib	Altretamine	Carmustine
Busulfan	Catumaxomab	Azacitidine	Cisplatin
Chlorambucil	Cetuximab	Bendamustine	Cyclophosphamide (>1.5 g/m^2)
Cladribine	Cytaribine (<1 gm/m^2)	Clofarabine	Dacarbazine
Cytaribine (<100 mg/m^2)	Docetaxel	Carboplatin	Lomustine
Fludarabin	Doxorubicin liposomal	Cyclophosphamide (≤1.5 g/m^2)	Mechlorethamine
Hormones	Etoposide	Cytarabine (>1 g/m^2)	Pentostatin
Hydroxyurea	5-Fluorouracil	Daunorubicin	Streptozocin
Interferon	Gemcitabine	Doxorubicin	
Mercaptopurine	Ixabepilone	Epirubicin	
Methotrexate (<100 mg/m^2)	Methotrexate (>100 mg/m^2)	Idarubicin	
Thioguanine	Mitoxantrone(<12 mg/m^2)	Ifosfamide	
Vinblastine	Paclitaxel	Irinotecan	
Vincristine	Panitumumab	Melphelan	
Vinorelbine	Pegasparaginase	Mitoxantrone(>12 mg/m^2)	
	Pemetrexed	Oxaliplatin	
	Teniposide	Temozolamide	
	Thiotepa	Treosulphan	
	Topotecan	Trabectedin	
	Trastuzumab		
*Percentages indicate the risk of vomiting with intravenously administered antineoplastic agents in the absence of antiemetic prophylaxis; Data from Jordan et al. (2007), Kris et al.(2006), Roila et al. (2006,2010).			
Oral			
Chlorambucil	Capecitabine	Cyclophosphamide	Hexamethylmelanine
Erlotinib	Etoposide	Imatinib	Procarbazine
Gefitinib	Everolimus	Temozolamide	
Hydroxyurea	Fludarabine	Vinorelbine	
Melphalan	Lapatinib		
Methotrexate	Lenalidomide		
Sorafenib	Sunitinib		
6-Thioguanine	Thalidomide		
*Percentages indicate the risk of vomiting with intravenously administered antineoplastic agents in the absence of antiemetic prophylaxis; Data from Jordan et al. (2007), Roila et al. (2006, 2010).			

antiemetic treatment (Gralla et al., 1999).

Dose intensity: The more frequently treatment is given, the more severe nausea might be. This dose-intensive therapy is better at curing cancer, but can also increase the severity of side effects.

Agents: Certain drugs tend to cause more nausea and vomiting than others. Among the worst culprits are Platinum (cisplatin) and Adriamycin (doxorubicin). Both are given intravenously-injected with a needle into a vein.

Target site: Treatment in the brain and gut causes more nausea and vomiting than in other areas of the body. The nerve impulses that trigger nausea and vomiting are in the brain.

Administration: Chemotherapy injected into a vein (intravenously) tends to cause more nausea than pills.

Gender: Women are more apt to experience nausea than men. "*This might be due to women's hormonal changes and emotions*".

Hyperemesis: Women who had significant nausea and vomiting during pregnancy are more likely to have these same side effects when undergoing cancer treatment.

Age: Patients younger than 30 years tend to experience more nausea than older folks. Older people have a higher tolerance because of previous exposure to various toxins over their lifetime.

Alcohol and drug use: People who don't drink alcohol or take prescription drugs might have more nausea because they are not used to chemical alterations occurring in their bodies. A few types of chemotherapies actually contain alcohol.

History: People who are prone to motion sickness may be more likely to have nausea and vomiting during treatment.

Antiemetic Prophylaxis Prevention of Acute Nausea and Vomiting

Before chemotherapy, it is crucial to clearly define the optimal prophylactic antiemetic therapy for acute and delayed nausea and vomiting and to implement it from the beginning, since symptom-oriented therapy at later stage is ineffective in most cases. This is important especially for the prophylaxis of delayed emesis. Emetogenic potential of the planned chemotherapy regimen needs to be established first. For patients who are taking chemotherapy on outpatients, it is important to decide treatment plan for the prophylaxis of delayed emesis.

Highly emetogenic chemotherapy

Patients should be treated with combination of 5-HT3-RA, a NK-1-RA (Aprepitant) and a corticosteroid.

Moderately emetogenic chemotherapy

Patients receiving AC chemotherapy for breast cancer should be treated with combination of 5-HT3-RA, a NK-1-RA (Aprepitant) and a corticosteroid. If Aprepitant is not available, women should receive a combination of Palanosetron plus dexamethasone (Roila et al., 2010)

Patients undergoing other moderately emetogenic chemotherapy should be given combination of with combination of 5-HT3-RA palanosetron and a corticosteroid dexamethasone.

Low emetogenic chemotherapy

Patients receiving low emetogenic chemotherapy should be treated with single agent such as low dose of corticosteroid. Patients of this group should not be overtreated with 5-HT3-RA routinely.

Minimally emetogenic chemotherapy

No antiemetic drug should be routinely administered before chemotherapy.

Prevention of Delayed Nausea and Vomiting

The presence of delayed emesis is often underestimated, with the consequence that no adequate preventive measures are taken.

Highly emetogenic chemotherapy

Routinely, Patients are treated with combination of NK-1-RA (Aprepitant) and a corticosteroid. The addition of 5-HT3-RA is not necessary most of the time (Schmoll et al., 2006).

Moderately emetogenic chemotherapy

Aprepitant or Fosaprepitant should be used to prevent delayed nausea and vomiting. A patient who has received Palanosetron for acute emesis, dexamethasone treatment is the preferred treatment for prevention of delayed nausea and vomiting. Patients can also be considered for multiday oral dexamethasone treatment for prevention of delayed emesis.

Low and minimally emetogenic chemotherapy

No prophylactic antiemetic treatment is planned for delayed emesis.

Therapy against Anticipatory Nausea and Vomiting (ANV)

ANV is a learned conditional reflex and drug therapy has modest efficacy. It may be best managed by psychological techniques, although this may not represent an easy solution in our day to day practice. The best approach is to avoid this by using optimal antiemetic prophylaxis from the first cycle. Conventional antiemetic are mostly ineffective however treatment with benzodiazepines in addition to conventional therapy has shown some efficacy if given before chemotherapy. Muscle relaxation, systemic desensitisation, hypnosis and cognitive distraction are possible interventions but its usefulness is doubtful.

Therapy in Cases of Insufficient Antiemetic Efficacy

If patient presents with emesis despite of preventive measures, it should first be checked that patient received the antiemetic according to guidelines. In general, a

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Table 2. Doses and Schedules of Antiemetic Agents with a High Therapeutic Index

Drug	Dose	
	Before Chemotherapy (day 1)	After Chemotherapy
High*		
Dolasetron (Anzemet, Sanofi-Aventis)	Intravenous dose: 100 mg or 1.8mg/kg of body weight; oral dose: 100 mg	Oral dose: 100 mg on days 2 and 3 for MEC with potential for delayed emesis
Granisetron (Kytril, Roche)	Intravenous dose: 1 mg or 0.01 mg/kg; oral dose: 2 mg	Oral dose: 1 mg twice daily on days 2 and 3 for MEC with potential for delayed emesis
Ondansetron (Zofran, GlaxoSmithKline) I	Intravenous dose: 8 mg or 0.15 mg/kg; oral dose: 24 mg for HEC, 8 mg twice daily for MEC	Oral dose: 8 mg twice daily on days 2 and 3 for MEC with potential for delayed emesis
Palonosetron (Aloxi, MGI Pharma)	Intravenous dose: 0.25 mg	
Tropisetron (Navoban, Novartis)	Intravenous dose: 5 mg; oral dose: 5 mg	Oral dose: 5 mg on days 2 and 3 for MEC with potential for delayed emesis
Dexamethasone		
With aprepitant or fosaprepitant	Intravenous dose: 12 mg; oral dose: 12 mg	Oral dose: 8 mg twice daily on days 2-4 for HEC, 8 mg on days 2 and 3 for MEC with potential for delayed emesis
Without aprepitant or Fosaprepitant	Intravenous dose: 20 mg for HEC, 8 mg for MEC; oral dose: 20 mg for HEC, 8 mg for MEC	Oral dose: 8 mg twice daily on days 2-4 for HEC, 8 mg on days 2 and 3 for MEC with potential for delayed emesis
Fosaprepitant (Emend [for injection], Merck)	Intravenous dose: 115 mg	Oral dose: 80 mg on days 2 and 3
Aprepitant (Emend [capsules], Merck)	Oral dose: 125 mg	Oral dose: 80 mg on days 2 and 3
* HEC denotes highly emetogenic chemotherapy, and MEC moderately emetogenic chemotherapy.		
Low**		
Metoclopramide (Reglan, Baxter and Alaven)	Intravenous dose: 1-2 mg/kg of body weight*	Intravenous dose: 1-2 mg/kg 2 hr after chemo¬therapy; oral dose: 0.5 mg/kg every 6 hr on days 2-4
Prochlorperazine (Compazine, GlaxoSmithKline)	Intravenous dose: 5-10 mg; oral dose: 5-10 mg	Oral dose: 5-10 mg every 6 hr as needed
Dronabinol (Marinol, Solvay)	Oral dose: 5 mg/m² of body-surface area	Oral dose: 5 mg/m² every 2-4 hr as needed
Nabilone (Cesamet, Valeant)	Oral dose: 1-2 mg	Oral dose: 1-2 mg twice daily or as needed
Olanzapine (Zyprexa, Eli Lilly)	Oral dose: 5 mg daily for 2 days preceding chemotherapy; 10 mg on day 1	Oral dose: 10 mg on days 2-4
**This dose is for use only in patients who cannot tolerate or do not have a response to 5-HT3-receptor antagonists, dexamethasone, and aprepitant, given the risk of adverse neurologic events with this higher dose of metoclopramide		

repetition of the previously given antiemetic agents usually does not produce the desired result. This is true particularly for first generation 5-HT3-RAs (Musso, 2009). It has been suggested that in view of different mechanism of action, addition of palanosetron will be a better rationale (Einhorn, 2010). For patients, who received a combination of a 5-HT3-RA with a corticosteroid, a NK-1-RA (Aprepitant/Fosaprepitant) should be added.

With lasting emesis the addition of metaclopromide, benzodiazepines, and neuroleptic agents and in particular olanzapine may be effective (Hesketh, 2008). The following drugs/doses can be used with caution in frequently sedated patients.

Metaclopromide	10 mg IV or 20-40mg PO every 4-6 hours
Olanzapine	5-10 mg once
Benzodiazepine	Lorazepam: 1mg tablet one or two, Alprazolam: 0.25-1 mg tablet
Domperidone	10-20 mg PO 3-4 times a day, Max.Daily dose 80 mg
Haloperidol	0.5-2 mg PO 8-12 hourly, 1-2 mg short IV infusion
Promethazine	25-50 mg PO 3-4 times a day
Chlorpromazine	25-50 mg slow IV
Dronabinol	5-10 mg PO every 3-6 hours, Max. daily dose 50 mg

PO: Per oral, IV: Intravenous

In addition, other conditions like emetogenic drug therapy, brain metastasis and gastrointestinal obstructions leading to continuous emesis should be ruled out.

Therapy in Multiple Day chemotherapy

For multiple day cisplatin therapy, the use of a 5-HT3-RA and a corticosteroid is recommended on the days when cisplatin is administered to the patients (Acute phase). In addition, for prophylaxis of delayed emesis, a corticosteroid alone should be administered. Aprepitant may be useful for multi-day chemotherapy regimens that are likely to be highly emetogenic. Use of 5-HT3-RA an day 1-5 or Palanosetron on days 1, 3, 5 is also recommended (Roila et al., 2010).

Therapy in High Dose Chemotherapy

On the day when high-dose chemotherapy is administered (acute phase), the use of a 5-HT3-RA and a corticosteroid is recommended before initiation of chemotherapy. On days 2-3 after high dose chemotherapy, a corticosteroid alone should be given for prevention of delayed nausea and vomiting. The addition of NK-1 RA or use of Palanosetron can be taken into consideration, although not recommended by recent guidelines.

Novel Therapy

Netupitant: Netupitant is a highly selective NK1 receptor antagonist, which is thought to work by blocking the action of substance P, an endogenous neurotransmitter contained in high concentrations in the vomiting center of the brainstem that can stimulate the vomiting reflex. Netupitant is currently under phase III trials.

Akynzeo: this is a fixed combination capsule of Netupitant and palanosetron, which is currently in Phase III trials helps in preventing CINV. The blockage of P/NK1 receptors by Netupitant in the central nervous system inhibits the binding of endogenous tachykinin neuropeptide substance and this result in preventing the chemotherapy-induced nausea and vomiting. Moreover, Palonosetron helps in the blockage of serotonin at 5-hydroxytryptamine type 3 (5-HT3) receptors and it also helps in the chemotherapy-induced nausea and vomiting. USA FDA approved this drug on 10th October, 2014 for treatment of CINV.

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